NOVEL APOPTOSIS PROTEINS

This is a 371 of PCT/US99/17776 filed 08/06/1999, which claims benefit of 60/099,496 filed 09/08/1998, 60/095,590 filed 08/06/1998, and 60/095,587 filed 08/06/1998.

FIELD OF THE INVENTION

The invention relates to novel methods and compositions of apoptosis proteins, collectively termed "Apop proteins", and nucleic acids encoding them. The invention further relates to methods of screening for bioactive agents that bind to and modulate Apop protein function for the diagnosis and treatment of disease.

BACKGROUND OF THE INVENTION

Apoptosis, or programmed cell death, is a highly ordered, genetically controlled process which plays a vital role in both healthy and disease states, including embryogenesis, tissue homeostasis and remodeling, cancer, autoimmune disorders, viral infections, and certain degenerative disorders.

The death domain of TNF receptor-1 (TNFR1) triggers distinct signaling pathways leading to apoptosis and activation of the NF-κB transcription factor through its interaction with the C-terminal death domain of TRADD, a 34 kDa cytoplasmic protein [see Hsu et al., Immunity 4:387-96 (1996)]. TRADD interacts strongly with RIP (receptor-interacting protein; Stanger et al., Cell 81:513-23 (1995), a 74 kDa serine-threonine kinase that with a C-terminal death domain involved in apoptosis; RIP also activates NF-κB. A second RIP protein, RIP2 or RICK [see McCarthy et al., J. Biol. Chem. 273:16968 (1998) and Inohara et al., J. Biol. Chem. 273:12296 (1998)] also contains a death domain and activates NF-κB.

A characteristic feature of apoptosis is activation of a cascade of cytoplasmic proteases that results in the cleavage of selected target proteins. ICE (interleukin 1 beta-converting enzyme) family proteases, also known as caspase proteases, initiate the active phase of apoptosis by degrading specific structural, regulatory, and DNA repair proteins within the target cell [Lazebnik et al., Nature 371:346-7 (1994); Casciola-Rosen et al., J. Biol. Chem. 269:30757-60 (1994)]. For example, a RIP-like kinase, termed CARDIAK/RICK or RIP2 [see Thome et al., Current Biol. 8:885-88 (1998); McCarthy et al., J. Biol. Chem. 273:16968-75 (1998); Inohara et al., J. Biol. Chem. 273:12296-300 (1998)] has been shown to associate with caspase-1. These caspases are related to the *C. elegans* cell death gene product. Caspases are cysteine proteases that display aspartate specificity, and have been shown by a number of researchers to be crucial to apoptotic pathways. For a review, see Cryns et al., Genes & Development 12:1551-70 (1998). The natural substrates of the caspases are key regulatory and